Implications of using the international recognition procedure (IRP) for a NICE technology appraisal evidence submission

## Background

1. From 1 January 2024, companies can apply for a Great Britain (GB) marketing authorisation using the Medicines and Healthcare products Regulatory Agency (MHRA) international recognition procedure (IRP). This procedure uses trusted international reference regulators to allow medicines to be approved based on their assessment reports. But using the IRP could affect the types of evidence available for the NICE evaluation. This document provides guidance to companies on the minimum evidence requirements for a NICE evaluation.
2. [NICE’s health technology evaluations manual](https://www.nice.org.uk/process/pmg36) (PMG36) sets out the process for and the evidence needed for NICE to be able to evaluate a medicine. PMG36 will apply regardless of the route used to obtain a GB marketing authorisation. As such, evidence requirements for a NICE evaluation will not change depending on what regulatory approval route is used.
3. The IRP provides an opportunity for companies to launch their products shortly after approval has been obtained in a different jurisdiction. NICE strives to publish final guidance within 90 days of the product receiving a marketing authorisation. This means that companies may need to make a NICE evidence submission before they submit to the MHRA, if NICE is to meet its target of publishing timely guidance, and patients are to benefit from timely access to medicines after a marketing authorisation is given.
4. There may be a time lag of months or sometimes years between the first global launch of a new medicine and the GB regulatory approval. The IRP offers companies the opportunity to consider launching their medicine in the UK earlier. Companies wishing to use the IRP immediately after regulatory approval in another country will need to consider whether this affects the evidence base that will be available for their NICE evaluation. For certain medicines, regulatory approval by other regulators can be granted based on an interim analysis of clinical trial data, especially when conditional or expedited regulatory pathways are used. Further analysis of data cuts will then be planned after the initial regulatory approval is received.
5. When the evidence supporting a medicine’s clinical effectiveness is immature at the time of the NICE evaluation, this can make the health technology assessment (HTA) of the medicine more challenging. HTA generally requires evidence about the long-term effectiveness of the medicine. When the HTA needs to take place before the clinical trial has been completed, such evidence can be lacking, which can pose challenges to decision making.
6. There are more considerations related to the evidence package that will be available to inform the NICE evaluation, for example using surrogate endpoints, the availability of long-term extension studies, what comparators were included in the clinical trial, and the outcomes that were measured. The following section is an overview of points to consider and possible mitigation strategies for companies considering using the IRP.

## Using the IRP immediately after the first regulatory approval in another country has been received

### Scenario 1: proceed as planned

1. NICE encourages companies to consider using this route if all of the following criteria can be met:
   1. The company has notified NICE of its intention to launch in the UK on time (24 months before expected GB marketing authorisation).
   2. The company is able to provide a complete evidence submission, in line with [NICE’s health technology evaluations manual](https://www.nice.org.uk/process/pmg36), by the deadline provided by the NICE scheduling team, even if this would fall before the company would have to submit its application to the MHRA.
   3. The final analysis of the company’s randomised controlled trial (RCT) is available at the time of submission to NICE, with no further analysis of the clinical trial planned (not including any long-term extension studies).
   4. The population in the clinical trial is broadly representative of the population likely to have treatment in the NHS, and the comparators (if relevant) align with standard care in the UK, or a robust indirect treatment comparison is possible.
   5. The clinical trial showed efficacy using a well-established clinical endpoint. When a surrogate endpoint is used, the endpoint has been validated as set out in [sections 4.6.6 to 4.6.11 of NICE’s health technology evaluations manual](https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation-2#modelling-methods).
2. When companies plan a cost-comparison analysis and the clinical trial evidence meets the criteria set out above, NICE encourages companies to consider using the IRP shortly after approval in another country has been received.

### Scenario 2: proceed with caution

1. Companies might still want to use the IRP immediately after approval in another country has been received without meeting all of the criteria in scenario 1. In such circumstances, NICE suggests that companies might want to consider the following situations and risk mitigation strategies.

#### Criterion C not met: regulatory approval was based on primary endpoint analysis or an interim analysis, and further analyses of the clinical trial data are planned in the future

1. In this situation, the company might still want to proceed with the IRP and NICE submission if it can meet all of the other criteria in scenario 1. The company should explore if this might make the medicine a good candidate for managed access. If it is, then NICE would encourage companies to consider using the IRP and to submit a managed access proposal with the NICE submission.
2. Companies should keep in mind the specific commercial requirements for entry into managed access, as well as the specific commercial arrangements for the Cancer Drugs Fund and the Innovative Medicines Fund. These are explained in the [Innovative Medicines Fund Principles](https://www.england.nhs.uk/publication/the-innovative-medicines-fund-principles/) and [Cancer Drug Fund Principles](https://www.england.nhs.uk/cancer/cdf/).

#### Criterion C not met: regulatory approval was based on a single-arm study

1. In this situation, the company might still want to proceed with the IRP and NICE submission if it can meet all of the other criteria. If the company has received conditional approval and there is an ongoing RCT, the company should explore whether this makes the medicine a good candidate for managed access. Paragraphs 10 and 11 apply.
2. If there is no RCT or no further RCT evidence generation planned, the company will need to carefully consider if the evidence base will be sufficient for a NICE evaluation shortly after regulatory approval. The following factors will influence the likely uncertainty in the clinical- and cost-effectiveness evidence:
   1. The length of follow up in the clinical trial.
   2. The sample size of the trial and whether the trial population broadly represents people who are likely to have treatment in the NHS.
   3. The availability of good natural history data that could be used for creating a synthetic control arm. Here, the principles in NICE Decision Support Unit (DSU) [Technical Support Document 17](https://www.sheffield.ac.uk/nice-dsu/tsds/observational-data) and the [NICE real-world evidence framework](https://www.nice.org.uk/corporate/ecd9/chapter/overview) need to be followed to generate good-quality comparative data.
3. It is difficult to indicate whether under these circumstances, companies should consider mitigation strategies that could reduce the uncertainty. If long-term follow up in the trial or a long-term extension study is planned, this could make the medicine a candidate for managed access (see paragraphs 10 and 11). But if the final follow-up data from the trial is likely to become available in the short term, companies might want to plan their regulatory approval and NICE submission such that they can make optimal use of the evidence when it is available.

#### Criterion D not met: the trial population does not align with NHS practice, or the comparators do not align with standard care in the UK

1. Clinical trials may be done in international settings that do not reflect NHS practice in terms of the population recruited, the treatment options available, or the care provided alongside the treatment under consideration. Clinical trial populations rarely reflect the target population so well that they could be regarded as a representative sample of it. So the generalisability and applicability of trial results are always a matter of judgement. As well as providing full details of the trial’s eligibility criteria, people recruited and excluded, and concurrent treatments, companies may wish to provide real-world evidence on the characteristics of the target population to support the assessment of the external validity of the results.
2. If an RCT uses a comparator that is not used in NHS practice, indirect comparisons and network meta-analyses should be done (see [sections 3.4.11 to 3.4.21 of the NICE health technology evaluations manual](https://www.nice.org.uk/process/pmg36/chapter/evidence#synthesis-of-evidence)). These techniques are most reliable when there is a connected network of randomised trials with common comparators and little difference between the trials in the distribution of treatment-effect modifiers. When this is not the case, population-adjustment methods using individual patient data from the pivotal trial may be used (see the NICE DSU [Technical Support Document 18](https://www.sheffield.ac.uk/nice-dsu/tsds/evidence-synthesis)).
3. ‘Unanchored’ indirect comparisons should only be used if there is a disconnected network or single-arm trials. Unanchored comparisons based on disconnected networks or involving single-arm studies assume that absolute treatment effects are constant at any level of the effect modifiers and prognostic variables, and that all effect modifiers and prognostic variables are known. These assumptions are problematic, so if an unanchored comparison is presented, it should be accompanied by an attempt to quantify the possible extent of any residual systematic error resulting from unobserved prognostic variables and effect modifiers.

#### Criterion E not met: regulatory approval was based on a non-validated surrogate endpoint

1. Some regulatory routes, such as the US Food and Drug Administration (FDA)’s accelerated approval, allow the use of surrogate endpoints with less evidentiary support, when they are considered reasonably likely to predict a clinical benefit. When the approval is based on a non-validated surrogate endpoint (defined by [sections 4.6.6 to 4.6.11 of NICE’s health technology evaluations manual](https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation-2#modelling-methods)), this can cause challenges for a NICE evaluation, because cost-effectiveness models require the relationship between the surrogate endpoint and long-term outcomes to be modelled. Evidence needs to be available to support this modelling. How challenging this will be for cost-effectiveness modelling will depend on:
   1. what secondary endpoints were included in the trial that could be used to measure changes in health outcomes relevant to HTA
   2. how the trial data will be used in the economic model
   3. what assumptions will be needed about the relationship between the medicine’s effect on the endpoint and longer-term outcomes, and whether that evidence is available or not
   4. what the medicine’s value proposition is: is it primarily improving health-related quality of life by improving symptoms; or is it disease modifying, meaning assumptions will be needed about the medicine’s longer-term effects, which may or may not be observed during the trial period?
2. Several factors will affect whether this scenario will result in a challenging NICE evaluation. But importantly, this will depend on the size of the treatment effect, how clinically significant the treatment effect is, and how well understood the relationship is between the treatment effect as measured by the surrogate endpoint and long-term effects on health-related quality of life and survival. NICE encourages using [NICE Advice](https://www.nice.org.uk/about/what-we-do/life-sciences/nice-advice-service) services to explore risk mitigation strategies in more detail before companies decide on a route to approval in the UK.
3. NICE and several other HTA organisations are developing guidance on using surrogate outcomes in cost-effectiveness analyses (see ‘[How ‘surrogate outcomes’ influence long-term health outcomes](https://www.nice.org.uk/news/blogs/how-surrogate-outcomes-influence-long-term-health-outcomes)’ for more information). Detailed guidance is expected later in 2024.

## Final considerations

1. As with all routes to marketing authorisation, companies exploring whether to use the IRP will need to consider if the evidence package that will be available at the time of the NICE evaluation will be in line with the requirements in the [NICE health technology evaluations manual](https://www.nice.org.uk/process/pmg36). NICE encourages companies to use [NICE Advice](https://www.nice.org.uk/about/what-we-do/life-sciences/nice-advice-service) services to gain a better understanding of the extent their evidence generation plans can support a NICE evaluation of their medicine.
2. When deciding whether to use the IRP immediately after the first approval in another country, companies will need to consider the possible increased uncertainty in the clinical evidence caused by shorter follow-up periods, their willingness to use a patient access scheme to mitigate the impact of that uncertainty, and their willingness to submit a proposal for managed access.